Mechanistic rationale for targeting the unfolded protein response in pre-B acute lymphoblastic leukemia.

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Public Summary:
The unfolded protein response (UPR) pathway, a stress-induced signaling cascade emanating from the endoplasmic reticulum (ER), regulates the expression and activity of molecules including BiP (HSPA5), IRE1 (ERN1), Blimp-1 (PRDM1), and X-box binding protein 1 (XBP1). These molecules are required for terminal differentiation of B cells into plasma cells and expressed at high levels in plasma cell-derived multiple myeloma. Although these molecules have no known role at early stages of B-cell development, here we show that their expression transiently peaks at the pre-B-cell receptor checkpoint. Inducible, Cre-mediated deletion of Hspa5, Prdm1, and Xbp1 consistently induces cellular stress and cell death in normal pre-B cells and in pre-B-cell acute lymphoblastic leukemia (ALL) driven by BCR-ABL1- and NRAS(G12D) oncogenes. Mechanistically, expression and activity of the UPR downstream effector XBP1 is regulated positively by STAT5 and negatively by the B-cell-specific transcriptional repressors BACH2 and BCL6. In two clinical trials for children and adults with ALL, high XBP1 mRNA levels at the time of diagnosis predicted poor outcome. A small molecule inhibitor of ERN1-mediated XBP1 activation induced selective cell death of patient-derived pre-B ALL cells in vitro and significantly prolonged survival of transplant recipient mice in vivo. Collectively, these studies reveal that pre-B ALL cells are uniquely vulnerable to ER stress and identify the UPR pathway and its downstream effector XBP1 as novel therapeutic targets to overcome drug resistance in pre-B ALL.

Scientific Abstract:
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